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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/284,683	06/24/1999	GREGOR CEVC	500.1007	2670

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 07/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/284,683	CEVC, GREGOR	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-33,49-75,77-89 and 92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-33,49-75,77-89 and 92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 5-1-06 is acknowledged.

Claims included in the prosecution are 22-33 and 49-75, 77-89 and 92.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 22-33 and 49-92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 22 and 53 are confusing. Presumably the suspending medium is an aqueous medium and the amphiphilic components are phospholipids as determined by claims 73 and 78-80. If so, what is meant by 'solubility of the second amphiphilic component ----- is at least ten times greater than the solubility of the first amphiphilic lipid components. The phospholipids are insoluble in water. Also unclear as to what applicant intends to convey by 'further selected such that the permeation capability of the vesicles increases disproportionately or nonlinearly under increasing pressure'. Where are the vesicles permeated? In a subject or in vitro?

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that phospholipids are lipids, in their simplest form, are composed of glycerol bonded to two fatty acids and a phosphate group and that the resulting compounds contains a region that is fat soluble and a region that is water soluble. This argument is not persuasive since the resultant compound is still not

soluble in water. A group on a molecule could be hydrophilic, but it does not make the group soluble in water since group by itself doesn't exist. The hydrophilic group on the phospholipid makes it orient toward water when hydrated. The examiner cites Merck Index which states that lecithin which is a phospholipid is insoluble in water in this context. With regard to the issue of permeation capability raised by the examiner, applicant points out to section 0015; there is no section 0015 in the specification.

'for example' renders claim 23 indefinite. This rejection is maintained since applicant deletes 'example water', but the term, 'for' is not deleted.

What is being conveyed through this claim? This claim is still confusing; the particle sizes of water depends upon the size of the liposomes and it is unclear what applicant means by 'which are smaller than the constrictions in the barrier'. The rejection is maintained.

What is being conveyed by 'comminuting' as applicable to vesicles in claim 24? Furthermore, it is unclear as to how one can determine the stability and permeation capability are determined by controlled mechanical whirling up, shearing and comminuting. Applicant amends the claim by introducing the term, 'or' after 'and'. It is unclear how this can overcome the issue raised by the examiner, that is, how one can determine these by controlled mechanical whirling up, shearing and comminuting.

What is being conveyed by through claim 32? Applicant amends the claims to introduce the term, 'have'. The amended expression which now reads as 'after the liquid droplets have formation'. What is being conveyed by this expression?

What is being deleted in claim 33 to overcome the issues? The line markings are not clear.

The Markush members recited in claim 80 are moieties and not amphiphilic lipids. Applicant appears to have misunderstood the issue. What are recited are groups on a compound. For example myristoleoyl is a moiety on a compound and not compound itself and being a hydrophobic moiety, it is not soluble in water at all and not' less soluble' as recited in the claim.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 53-75 and 77-89 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-35 of U.S. Patent No. 6,165,500. Although the conflicting claims are not identical, they are not patentably distinct from each other because for the following reasons. Instant claims are drawn to treatment of a mammal by administering the same transfersomes to the skin or mucous membrane of the mammal. Since the transfersomes have to be transported through the skin as claimed in patented claims, instant claims encompass the patented claims. Instant claim 53 is generic with respect to the amount of the lipid and the lipid: surfactant ratios in patented claims.

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicants argue that the patent describes transfersomes comprising a pharmaceutically acceptable lipid and a pharmaceutically acceptable surfactant contained in a pharmaceutically acceptable medium and there is absolutely no teaching or suggestion anywhere of a transfersome comprising at least two physiochemically different amphiphilic components differing in solubility in the liquid suspension medium by a factor of at least 10 as set forth in applicant's claim. This argument is not persuasive since the claims in said patent recite first lipid which is a phospholipid and the second component which applicant calls as surfactant contains sorbitane phospholipid, a monolaurate phospholipid, a lysophospholipid and fatty acid salts which

would read on instant claims since the solubilities of each of these differs from the first phospholipid recited. The rejection is maintained.

5. Claims 22-33 and 49-75, 77-89 and 92 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 69-87 and 101-103 of copending Application No. 10/357,618. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims 22-33 and 92 and the claims 69-79 are drawn to a method of preparation of same transfersomes; instant claim language does not exclude the presence of the third substance in the method of preparation and the generic claim 69 in said copending application encompasses instant molar amounts. Instant claims 49-91 are drawn to a method of treatment using the transfersomes and thus encompasses 'a method for generating a therapeutic effect on a warm blood creature applying transfersomes; as stated above, instant claim language does not exclude the presence of the third substance in the composition used in the method of generating a therapeutic effect in the claims of said copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicant argues that upon entry of the instant amendment and response, the provisional double patenting rejection will be the only rejection remaining in instant application and therefore, that this rejection be withdrawn so that the instant application

may proceed to allowance. This argument is not persuasive since this rejection is not the only rejection in instant application.

Claim Rejections - 35 U.S.C. § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 22-30, 32, 49-50 and 92 are rejected under 35 U.S.C. 102(b) as being anticipated by Blume et al of Record (Journal of Liposome Research 1992).

Blume et al disclose vesicles of instant invention. The method of preparation of the vesicles involves selecting the lipids DSPE (first lipid) and DSPE-triazine PEG110, mixing them and then sonicating the mixture. The compositions further contain an active agent (abstract, pages 357 and 358). Blume et al disclose the average diameter of the vesicles to be 100 nm (50 nm radius). Therefore, the presence of vesicles in claimed size range in claims 64-66 in Blume is implicit. Blume et al also do not disclose the claimed functional properties of their vesicles or the amphiphilic components. However, since the vesicles of Blume et al contain the same components, claimed properties are inherent.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Blume at least fails to teach or suggest a method for producing a preparation for transporting at least one active ingredient through the skin or mucous membrane of a mammal comprising selecting the first amphiphilic lipid component and a second amphiphilic component, such that the solubility of the second amphiphilic component in the pharmaceutically acceptable suspending medium is at least ten times greater than the solubility of the first amphiphilic lipid component in said medium, and wherein independently of the concentrations of the first and second amphiphilic components and the active ingredient, no solubilization of the vesicles in the suspension occurs as set forth in the independent claim 22. This argument is not persuasive since Blume teaches a method involving two phospholipids, namely, phosphatidylcholine and DSPE-triazine PEG 10 which applicant also uses in Examples 1-4 on page 29 of the specification and therefore, the claimed properties are inherent in Blume.

Since applicant amends claim 53 to introduce the limitation that the preparation is applied to the skin and mucous membrane, method claims 53-84 and 87 are withdrawn from this rejection.

8. Claims 22-33 and 49-75, 77-89 and 92 are rejected under 35 U.S.C. 102(b) as being anticipated by EP 0 475 160 of record (English equivalent, US 6165,500).

EP discloses instant composition (transfersomes) containing a drug, amphiphilic lipids (such as PC and PG) and a surfactant (oleic acid) in instant amounts and a method of preparation (see the entire document and the English equivalent). The

Examples 32-39 show the amounts of the lipids and surfactant, which appear to fall within the claimed limits. Although the reference does not explicitly recite the claimed steps such as selecting the lipids, adopting the composition by adjusting the amounts of the soluble component and adjusting the concentration of the lipid, since one cannot come up with specific amounts of the components as seen in example 32-39 of the reference without experimentation, the claimed steps are deemed to be implicit.

Applicant's arguments with regard to method of preparation claims have been fully considered, but are found to be persuasive. Applicant's arguments are similar to those advanced for the rejection over Blume and therefore, the same reasoning is applicable. Applicant's arguments that Blume further fails to teach or suggest a non-invasive method of using a preparation in the form of vesicles suspended in a liquid medium as set forth in the independent claim 53 are not persuasive since these are method of use claims and irrespective of the method of preparation, the product is the same. The reference teaches a method of use of the product on the skin and therefore, it reads on instant claims. The rejection is maintained.

Claim Rejections - 35 U.S.C. § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 24-25, 31, 51-52, 68-75, 77-89 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blume et al cited above, further in view of EP 0 475 160 cited in the previous actions (English equivalent US 6,165, 500).

The teachings of Blume et al have been discussed above. What is lacking in Blume et al is the determination of the stability and permeation capability by filtration under pressure through a filter or by mechanical comminuting. Blume et al is also lacking instantly claimed amphiphilic drugs, non-steroidal anti-inflammatory drugs such as diclofenac and other drugs in instant claims.

EP while disclosing similar vesicular preparations teaches that permeation capability of the vesicles could be determined by these methods (columns 54-55). EP also discloses several drugs, which could be used in the vesicles (columns 19-32).

Measuring permeation capability of the vesicles of Blume et al or use of claimed drugs for encapsulation in the vesicles of Blume et al would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since EP shows that these are routinely practiced with the vesicular compositions.

Applicant provides no specific arguments for the rejection. The rejection is maintained.

11. Claims 22-33 and 49-75, 77-89 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0 475 160 cited above (English equivalent, US 6,165,500).

As pointed out above, EP teaches the same deformable transfersomes composition containing a drug, combination of amphiphilic lipids and a surfactant in instant amounts and a method of preparation. It is unclear whether the reference teaches all the instant functional parameters and mole percentages (since they are given in terms of weight). In case they are different, in the absence of showing the criticality, they are deemed to be parameters manipulatable by an artisan to obtain the best possible results.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments once again are based on the lack of mention of the solubility of either the lipid or surfactant in the prior art. These have been addressed above.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Woodward Michael can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

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G S Kishore

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK